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Clinical Investigation

Clinical and Hemodynamic Correlates and Prognostic Value of VE/VCO_2 Slope in Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Hypertension

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ABSTRACT

Background: Impaired exercise capacity is one of the hallmarks of heart failure with preserved ejection fraction (HFpEF), but the clinical and hemodynamic correlates and prognostic value of exercise testing in patients with HFpEF is unknown.

Methods: Patients with HFpEF (left ventricular ejection fraction [LVEF] ≥45%) and pulmonary hypertension underwent cardiopulmonary exercise test (CPX) to measure maximal (peak VO_2) and submaximal (ventilatory equivalent for carbon dioxide [VE/VCO_2] slope) exercise capacity. In addition, right heart catheterization was performed. Patients were grouped in tertiles based on the VE/VCO_2 slope. Univariate and multivariate regression analyses were performed. A Cox regression analysis was performed to determine the mortality during follow-up.

Results: We studied 88 patients: mean age 73 ± 9 years, 67% female, mean LVEF 58%, median N-terminal pro–B-type natriuretic peptide (NT-proBNP) 840 (interquartile range 411–1938) ng/L. Patients in the highest VE/VCO_2 tertile had the most severe HF, as reflected in higher New York Heart Association functional class and higher NT-proBNP plasma levels (all $P < .05$ for trend), whereas LVEF was similar between the groups. Multivariable regression analysis with backward elimination on invasive hemodynamic measurements showed that VE/VCO_2 slope was independently associated with pulmonary vascular resistance (PVR). Cox regression analysis showed that increased VE/VCO_2 slope (but not peak VO_2) was independently associated with increased mortality.

Conclusion: Increased VE/VCO_2 slope was associated with more severe disease and higher PVR and was independently associated with increased mortality in patients with HFpEF. (*J Cardiac Fail 2017;23:777–782*)

Key Words: VE/VCO_2 slope, heart failure with preserved ejection fraction, cardiopulmonary exercise test.

Approximately 50% of patients with heart failure have a preserved ejection fraction (HFpEF).[1] HFpEF is associated with high morbidity and mortality, and no evidence-based therapies are available for these patients.[2] Increased pulmonary arterial pressure is another important factor that is associated with the severity of HFpEF and consequently results in higher mortality.[3]

In addition to standard diagnostic tests, cardiopulmonary exercise testing (CPX) provides useful information regarding the clinical condition of patients.[4] Although peak VO_2 is the criterion standard in patients with heart failure, HFpEF patients often do not achieve peak VO_2 owing to elderly age and the presence of multiple comorbidities.[5] The VE/VCO_2 slope can be determined from submaximal exercise testing. Measurement of the slope of V_E versus V_{CO2} (VE/VCO_2 slope) during incremental exercise below the ventilatory compensation point is a prognostic indicator in patients with heart failure (HF) with reduced ejection fraction (HFrEF),[6]

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wbut the clinical characteristics and prognostic value of increased VE/VCO_2 slope in patients with HFpEF is unknown.[7] In the present study, we investigated the VE/VCO_2 slope during CPX in HFpEF patients to reveal its association with both invasive and noninvasive predictors and clinical outcome.

Methods

Study Design and Patient Selection

From October 2011 to September 2014, we retrospectively identified 102 patients with HFpEF based on heart failure symptoms (New York Heart Association [NYHA] functional class ≥II), left ventricular ejection fraction (LVEF) ≥45%, and signs of pulmonary hypertension on an earlier echocardiogram who were referred to the catheterization laboratory for routine left- and right-sided cardiac catheterization. At the same time as the catheterization, echocardiographic assessments were performed. Within 1 week after catheterization, exercise tolerance tests on a treadmill were carried out when patients were capable to do an exercise test, and during the exercise the VO_2 max test was performed. After these screening tests, a subset of the study patients were recruited for a single-center prospective randomized placebo-controlled trial investigating the effects of sildenafil in HFpEF with pulmonary hypertension.[8] Fifty-two of these patients were included in this trial, of which 26 were allocated to the sildenafil group.

Study Procedures

In all of the screened patients (n = 102), clinical and laboratory assessments were conducted regarding NYHA functional class, heart rhythm, medication usage, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and electrolyte plasma levels. In clinically stable patients, right-sided heart catheterization (HC) and simultaneous echocardiography were performed. These tests were executed by the same cardiologist and ultrasound technician in all of the patients. Echocardiographic parameters LV wall thickness, mitral valve velocities, tissue Doppler parameters, and systolic and diastolic ventricular end volumes were collected. During the right-sided HC the pressures in the right atrium, right ventricle, and pulmonary artery and in wedge position were obtained and cardiac output and pulmonary vascular resistance (PVR) calculated with the use of the Fick method. In 88 patients, CPX was performed; 14 patients were either not able or refused to undergo this procedure. All data points from the beginning of the exercise up to the ventilatory anaerobic threshold (VAT) were used to calculate the VE/VCO_2 slope.[9,10] Furthermore, if the determination of the VAT was difficult in the VE/VCO_2 slope, the VAT was also determined in the slope of the exhaled CO_2.[11] Peak VO_2 and respiratory quotient (RQ) ratio were measured.

Statistical Analysis

The patient population was divided into tertiles based on the VE/VCO_2 slope. Data are presented as median (interquartile range [IQR]) for nonnormally distributed data and as mean ± SD for normally distributed data or percentages. Differences between categoric groups were calculated with the use of the chi-square test. Differences between continuous variables were calculated with the use of the Kruskal-Wallis equality-of-populations rank test or 1-way analysis of variance where appropriate. To determine the factors relating to the VE/VCO_2 slope, a univariate linear regression model was performed. We performed one multivariable linear regression analysis with backward elimination including variables that showed a P value of <.1 in univariate analyses. Kaplan-Meier curves were constructed to determine the mortality in the 3 VE/VCO_2 tertiles with the use of the log-rank test of equality. Univariate and multivariable Cox proportional hazard regression models were used to calculate the predictive value of the VE/VCO_2 slope on a continuous scale and by tertiles on mortality. The proportional hazard assumption was checked by investigation of Schoenfeld residuals, and no violations were observed. A P value of <.05 was considered to be statistically significant. Analyses were conducted with the use of stata version 13 for windows (Statacorp, College Station, Texas).

Results

Baseline Characteristics

The baseline characteristics according to tertiles of VE/VCO_2 slope are presented in Table 1. In all patients, the mean age was 73 ± 9 years and 67% were female. The lowest tertile (25.0–33.0) and middle tertile (33.1–38.3) of VE/VCO_2 slope each consisted of 29 patients, and the highest tertile (38.4–89.0) consisted of 30 patients. Mean age did not differ among the 3 groups. The NYHA functional class did not differ among the tertiles (P = .064). NT-proBNP plasma levels were 599.5 ng/L (IQR 312.0–989.0) in the lowest tertile, 930 ng/L in the middle tertile (461–1615), and 1561 ng/L in the highest tertile (535.5–2479.0; P = .037). A subdivision of patients with and without atrial fibrillation was analyzed, and no differences were observed in that analysis regarding the VE/VCO_2 slope (P = .924).

Results of the peak VO_2 are presented in Table 2. Peak VO_2 did not differ among the VE/VCO_2 slope tertiles (P = .150). Interestingly, only 31 patients (35%) reached an RQ ratio of ≥1. The RQ ratio did not differ among tertiles.

Baseline invasive hemodynamic measurement results across the VE/VCO_2 slope tertiles are presented in Table 3. The lowest right ventricular systolic pressure (46 ± 15 mm Hg) was found in the lowest VE/VCO_2 slope tertile, and right ventricular systolic pressure was highest (57 ± 19 mm Hg) in the highest tertile (P = .011). Mean pulmonary artery pressure (mPAP) was highest (35 ± 12 mm Hg) in the highest tertile, was 29 ± 7 mm Hg in the middle tertile, and was lowest (29 ± 10 mm Hg) in the lowest tertile (P = .017).

Table 1. Baseline Characteristics

Characteristic	Total	VE/VCO_2 slope tertile			*P* Value
		Lowest	Middle	Highest	
n	88	29	29	30	
VE/VCO_2		25.0–33.0	33.1–38.3	38.4–89.0	
Age (y)	73 ± 9	73.3 ± 7.4	74.8 ± 8.4	71.7 ± 11.0	.430
Sex, male (%)	33	45	17	37	.071
NYHA functional classification (%)					.064
II	41	55	45	23	
III	57	45	55	70	
LVEF (%)	60.0 (55.0–60.0)	60.0 (55.0–60.0)	60.0 (57.5–60.0)	60.0 (55.0–60.0)	.540
SBP (mm Hg)	151.0 (134.0–165.0)	152.5 (140.5–161.0)	154.0 (135.0–171.0)	144.5 (128.0–162.0)	.270
DBP (mm Hg)	68.0 (60.0–78.0)	68.0 (63.0–73.5)	69.0 (60.0–79.0)	64.5 (56.0–79.0)	.720
Heart rate (beats/min)	71 ± 12	69 ± 12	70 ± 13	74 ± 11	.230
Body mass index (kg/m^2)	27 (25–31)	27.5 (24.7–33.2)	27.1 (25.0–30.7)	26.3 (24.2–29.4)	.350
Heart rhythm					.480
SR (%)	58	66	55	53	.600
AF (%)	33	24	38	37	.460
Medical history (%)					
Cerebrovascular disease	3	7	3	0	.340
AF	51	55	48	50	.860
Chronic	35	28	45	33	.380
Paroxysmal	17	28	7	17	.110
Diabetes mellitus	28	24	28	33	.730
Hypertension	65	69	62	63	.840
COPD	16	14	17	17	.930
Pacemaker	11	10	10	13	.920
Medical therapy (%)					
β-Blocker	78	76	90	70	.170
Diuretic	75	61	76	87	.074
ACE inhibitor	68	64	76	63	.520
Aldosterone blocker	30	21	31	37	.440
Calcium channel blocker	5	4	3	7	.800
Hemoglobin (mmol/L)	8.2 (7.5–8.6)	8.3 (7.8–8.7)	8.1 (7.5–8.6)	8.1 (7.1–8.7)	.680
Creatinine (μmol/L)	98.4 ± 37.9	96.2 ± 39.6	89.1 ± 26.4	110.6 ± 44.1	.097
eGFR (mL/min)	61.0 (44.0–73.0)	65.0 (52.0–77.0)	61.0 (45.0–78.0)	50.0 (32.0–68.0)	.260
Urea (mmol/L)	9.1 ± 4.5	7.6 ± 3.1	8.6 ± 4.1	11.2 ± 5.3	.006
Plasma NT-proBNP (ng/L)	840 (411–1938)	599.5 (312.0–989)	930 (461–1615)	1561 (535.5–2479)	.037
Sodium (mmol/L)	141 (138–143)	142.0 (139.5–144.0)	140.5 (138.0–142.0)	140.0 (137.0–142.0)	.120
Potassium (mmol/L)	4.2 (3.9–4.6)	4.3 (3.9–4.6)	4.2 (4.0–4.7)	4.2 (3.9–4.5)	.750
Mortality during follow-up (%)	18	14	14	30	.189

Normally distributed data are presented as mean ± SD, nonnormally distributed data as median (interquartile range), categoric variables as percentages of observations. VE/VCO_2, ventilatory equivalent for carbon dioxide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; SR, sinus rhythm; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Correlation Among Baseline Parameters and the VE/VO_2 Slope in HFpEF

Results of the univariate and multivariable regression analyses are presented in Table 4. Multiple significant correlations were observed between invasively measured pressures and the VE/VO_2 slope. mPAP was correlated with the VE/VCO_2 slope: correlation coefficient (CE) = 0.287; $P = .002$. When adjusted for age and log NT-proBNP, mPAP was still correlated with the VE/VCO_2 slope: CE = 0.233; $P = .027$. Even so, PVR was correlated with the VE/VCO_2 slope when adjusted for age and log NT-proBNP levels: CE = 0.015; $P = .024$. No correlation was observed between pulmonary capillary wedge pressure and the VE/VCO_2 slope: CE = 0.061; $P = .704$. After stepwise multivariable regression analysis of the invasive hemodynamic and the clinical variables with backward elimination, the only variable that remained independently associated with VE/VCO_2 slope was PVR.

Table 2. Peak VO_2 and respiratory quotient (RQ)

Measurement	Lowest VE/VCO_2 (25.0–33.0)	Middle VE/VCO_2 (33.1–38.3)	Highest VE/VCO_2 (38.4–89.0)	*P* Value
n	29	29	30	
Peak VO_2	14 ± 4	12 ± 3	12 ± 4	.150
RQ	0.96 ± 0.13	0.94 ± 0.11	0.91 ± 0.11	.436
RQ ≥1 (%)	35	38	33	.891

VE/VCO_2, ventilatory equivalent for carbon dioxide; VO_2, oxygen consumption.

The correlation between baseline parameters or invasively measured pressures and peak VO_2 could not be interpreted, because, as mentioned above, only 35% of the patients reached an RQ ≥1.

Survival Analysis

Sixteen (18%) patients died during a mean follow-up time of 2 ± 1 years. Increased VE/VCO_2 slope tertiles showed a

Table 3. Invasive Hemodynamic Measurements

Measurement	Total	Lowest VE/VCO_2 (25.0–33.0)	Middle VE/VCO_2 (33.1–38.3)	Highest VE/VCO_2 (38.4–89)	*P* Value
n	88	29	29	30	
RAM (mm Hg)	8.4 ± 4.9	7.6 ± 4.7	8.3 ± 4.2	9.3 ± 5.7	.380
RVS (mm Hg)	50.0 ± 16.5	46.3 ± 15.3	46.0 ± 11.2	57.2 ± 19.5	.011
RVED (mm Hg)	9.2 ± 4.5	8.3 ± 4.7	9.6 ± 3.4	9.7 ± 5.1	.380
sPAP (mm Hg)	49.0 ± 16.4	46.0 ± 15.7	44.7 ± 10.6	55.9 ± 19.5	.014
dPAP (mm Hg)	18.1 ± 6.9	16.7 ± 6.7	17.1 ± 5.5	20.3 ± 8.0	.088
mPAP (mm Hg)	31.0 ± 10.2	28.9 ± 9.8	28.7 ± 7.2	35.2 ± 11.7	.017
PH	65 (74)	19 (66)	22 (76)	24 (80)	.429
PCWP (mm Hg)	17.4 ± 6.1	16.0 ± 5.7	17.4 ± 5.3	18.8 ± 6.9	.210
PCWPdi	65 (74)	19 (66)	21 (72)	25 (83)	.291
LVS (mm Hg)	152.2 ± 22.2	153.9 ± 19.8	158.4 ± 22.4	144.1 ± 22.5	.056
LVED (mm Hg)	16.6 ± 5.8	15.1 ± 6.0	17.1 ± 5.1	17.5 ± 6.2	.310
AOS (mm Hg)	149.1 ± 22.6	151.6 ± 21.0	152.9 ± 23.6	143.2 ± 22.6	.210
AOD (mm Hg)	69.1 ± 12.8	70.3 ± 11.5	70.2 ± 13.1	67.1 ± 13.8	.570
AOM (mm Hg)	100.6 ± 14.3	101.7 ± 11.7	103.0 ± 16.1	97.1 ± 14.5	.250
PVR (dyne·s/cm^5)	212 ± 161	190 ± 156	175 ± 93	264 ± 201	.078

Normally distributed data are presented as mean ± SD, and categoric variables as n (%). RAM, mean right atrial pressure; RVS, right ventricular systolic pressure; RVED, right ventricular end-diastolic pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PH, pulmonary arterial hypertension; PCWP, mean pulmonary capillary wedge pressure; PCWPdi, PCWP as dichotomous variable, >16 cutoff; LVS, left ventricular systolic pressure; LVED, left ventricular end-diastolic pressure; AOS, aortic systolic pressure; AOD, aortic diastolic pressure; AOM, aortic mean pressure; PVR, pulmonary vascular resistance.

Table 4. Regression: Correlation With the VE/VCO_2 Slope

	Univariate Correlation Coefficients	*P* Value	Model 1	*P* Value
mPAP	0.287	.002	0.233	.027
sPAP	0.172	.003	0.134	.042
PVR	0.019	.002	0.015	.024
RVS	0.175	.002	0.134	.041
LVS	–0.123	.008	–0.107	.030
Sodium	–0.494	.092	–	–
Diuretic use	3.723	.091	–	–
Log NT-proBNP	0.917	.127	–	–
NYHA functional class	2.873	.145	–	–
Log urea	2.111	.173	–	–
Age	–0.130	.222	–	–
Sex	–2.084	.308	–	–
β-Blocker use	0.453	.847	–	–
LVED	–0.160	.281	–	–
PCWP	0.061	.704	–	–

Model 1: adjusted for log NT-proBNP and age. Abbreviations as in Tables 1 and 3.

trend toward increased mortality (*P* = .076). No differences were observed among the peak VO_2–based tertiles (*P* = .783).

In univariable analyses, the increase of VE/VCO_2 showed a significant increase risk for all-cause mortality (hazard ratio [HR] 1.92 [per 10 increase], 95% confidence interval [CI] 1.34–2.74; *P* < .001; Table 5). an association that was unaffected by adjustment for age and sex. When adjusted for independent predictors of outcome, including age, sex, PAP, renal function, NT-proBNP plasma levels, and atrial fibrillation, VE/VCO_2 slope was independently associated with an increased risk for all-cause mortality: HR 1.74 (per 10 increase), 95% CI 1.03–2.94; *P* = .040. When the same analysis was performed on peak VO_2, no association with all-cause mortality in either univariate (Table 5) or multivariable analysis was found: multivariable HR 1.42, 95% CI 0.39–5.24; *P* = .600).

Table 5. Cox Regression Analysis

	Univariate		Multivariable	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
VE/VCO_2				
Continuous (per 10 increase)	1.92 (1.34–2.74)	<.001	2.04 (1.42–2.93)	<.001
Lowest tertile	Ref	–	Ref	–
Middle tertile	1.44 (0.32–6.52)	.630	1.26 (0.28–5.82)	.760
Highest tertile	3.57 (0.96–13.3)	.060	4.11 (1.09–15.46)	.040
Peak VO_2				
Continuous (per 5 mL·min^{-1}·kg^{-2} decrease)	3.53 (1.29–9.62)	.014	3.49 (1.26–9.69)	.017
Highest tertile	REF	—	REF	—
Middle tertile	0.97 (0.21–4.39)	.960	0.96 (0.21–4.36)	.950
Lowest tertile	3.03 (0.78–11.8)	.110	2.93 (0.74–11.6)	.130

Model 1: adjusted for age and sex. Abbreviations as in Table 2.

Discussion

This study shows that increased VE/VCO_2 slope, established from submaximal exercise testing, is related to more severe disease and higher intracardiac and intrapulmonary pressures and had an independent association with increased mortality in patients with HFpEF and pulmonary hypertension. These associations were not found with peak VO_2, which was frequently not reached in these patients, as evidencde by an RQ <1.0 in 65% of the patients.

Although the mechanisms behind HFpEF are not fully understood, the main symptoms of the patients are shortness of breath and impaired exercise tolerance. These symptoms are not very specific for HFpEF. We therefore tried to identify independent predictors of the exercise capacity in HFpEF patients. Peak VO_2 is the criterion standard in CPX, so peak VO_2 is often used as the main parameter in exercise tolerance studies in HF.[12,13] Peak VO_2 depends on heart rate, stroke volume, and arterial-mixed venous oxygen content difference ($C[a\text{-}v]O_2$). Each of these 3 parameters, however, has been shown to be of limited use in HFpEF patients.[14] A reliable peak VO_2 measurement can be achieved only when patients perform at the maximum of their cardiopulmonary capacity, ie, achieve an RQ ratio ≥1.[5] However, most of the peak VO_2 measurements in our study were not reliable, because the RQ ratio ≥ 1 was not reached.[15] It should be noted that we included an elderly population with multiple comorbidities and with severe HFpEF with evidence of increased PAPs. In this elderly and diseased population, VE/VCO_2 slope was ideal to study exercise capacity even when peak VO_2 was not reached. VE versus VCO_2 is a linear relationship in incremental exercise. In the final phase of exercise, oxygen supply to the tissue is not sufficient and blood lactate concentration increases at a steep rate. At that point, the VAT, excess CO_2 is produced which results in a steeper bend of the VE/VCO_2 slope.[16] The linear relationship up to the VAT is a reliable measure for exercise capacity in HF patients because patients do not need to reach their maximum exercise capacity.[16,17]

A few studies have shown that increased VE/VCO_2 is associated with increased mortality in patients with HFrEF.[18] An overview by Guazzi described a solid base for the hypothesis that the VE/VCO_2 slope might be of prognostic value in HFpEF patients.[19] However, this is the 1st study on clinical and hemodynamic correlates and prognostic value of VE/VCO_2 slope specifically in patients with HFpEF. A few others studied the value of CPX in patients with HFpEF.[20–22] Guazzi et al compared CPX parameters with multiple variables between an HFrEF and an HFpEF population.[20] Although that study showed that the VE/VCO_2 slope represents HFpEF severity, no relationship between the VE/VCO_2 slope and mortality was studied. Cahalin et al studied the prognostic relevance of heart rate recovery after a 6-minute walk test in patients with HFrEF (n = 216) and HFpEF (n = 42). They showed that in the combined population with predominantly HFrEF patients, the VE/VCO_2 slope was a significant prognostic parameter in the 6-minute walk test, and they found that the VE/VCO_2 slope was the only predictor of major cardiac events.[21] Nedeljkovic et al studied the value of CPX as a diagnostic tool for HFpEF. They concluded that the VE/VCO_2 slope could be a reliable test to diagnose HFpEF in an early stage, but they did not investigate the possible association between VE/VCO_2 and mortality.[22]

Hemodynamic measurements in our study showed that increased VE/VCO_2 slope was associated with increased mPAP and PVR. Of note, no association was observed between VE/VCO_2 slope and PWCP. The VE/VCO_2 slope seems to be determined mostly by PAP and PVR and not PWCP. Guazzi et al also described a correlation between increased systolic PAP and a poorer VE/VCO_2 slope.[20] However, in contrast with Guazzi et al, we did not find a correlation between the echocardiographic parameters LVEF and E/E′ ratio and VE/VCO_2 slope. We hypothesize that this difference can be explained by the fact that our population was a more typical HFpEF population: older, mostly female, with higher levels of NT-proBNP and more severe HF. Differences in etiology of HFpEF can be seen between men and women: generally men are more prone to develop ischemic HF, in contrast to women where the abundance of comorbidities is seen as causing HFpEF.[23,24]

Study Limitations

The retrospective nature of this study is a limitation, and the relative small group size resulted in limited possibilities for multivariate analysis. Also, despite the predefined hypothesis to determine the diagnostic value of the VE/VCO_2 slope, the subanalyses were at risk of multiple testing uncertainties. To limit this risk, the multivariable regression analysis was performed with backward elimination. This study was not ideal for comparing peak VO_2 and VE/VCO_2 slope, because few patients reached an RQ ratio >1. A strong point of this study is the well defined HFpEF population and the simultaneously performed right-sided HC and echocardiography. However, these patients also showed echocardiographic signs of pulmonary hypertension, so the results cannot be extrapolated to the general HFpEF population.

Conclusion

In elderly patients with HFpEF, increased PAPs, and multiple comorbidities, peak VO_2 could often not be reached. In these patients, increased VE/VCO_2 slope (and not peak VO_2) was associated with more severe disease and higher intracardiac and intrapulmonary pressures and was independently associated with increased mortality.

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